

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 29 JUL 2004

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Applicant's or agent's file reference 4 -32435A	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/03470	International filing date (day/month/year) 02.04.2003	Priority date (day/month/year) 03.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D403/04		
Applicant NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 09.10.2003	Date of completion of this report 30.07.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31.70 340 - 3016	Authorized Officer Seitner, I Telephone No. +31 70 340-2389 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/03470**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-23 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 9,10 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 9,10 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-8
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/03470

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 9 and 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02 10158 A (HOFFMANN LA ROCHE) 7 February 2002 (2002-02-07)

D2: WO 01 46178 A (HOFFMANN LA ROCHE) 28 June 2001 (2001-06-28)

V.1. Novelty:

Document D1 which is considered to represent the closest prior art for the present compounds of formula I in which R is (a), discloses 3-indolyl-4-phenyl-1H-pyrrole-2,5-dione derivatives, which are useful for the treatment of GSK-3 β mediated diseases (see formula (I) of claim 1 as well as claims 18-34) such as Alzheimer's disease, atherosclerotic cardiovascular disease, immunodeficiency, cancer.

The compounds of D1 differ from the compounds of the present application in that the phenyl substituting the maleimid ring is further substituted by morpholine or N-pyrrolidine, whereas the present compounds are substituted by piperazine.

Therefore, the subject matter of claims 1-10 is considered as novel (Article 33(2) PCT) over the prior art.

V.2. Inventive Step:

The general formula (I) of the present application actually overlaps with the formula of D1, when R represents (a). Therefore, the present compounds represent a selection from a general formula of compounds whose activity is already linked to Alzheimer's disease, atherosclerotic cardiovascular disease, immunodeficiency, and cancer and it would have been obvious for the skilled person to choose a group of compounds within the general formula of D1 in order to provide further compounds for the treatment of said diseases.

Furthermore, D2 discloses a compound for the treatment of cancer (see example 12k as well as claims 38-45), which differ from the compounds of the present formula I in which R represents (b), (c), (d), or (e), in that the indolylmaleimide is substituted by a second indole ring, whereas the present indolylmaleimide compounds are further substituted by naphthyl, pyrimidine, quinoline or isoquinoline. However, the replacement of a heteroaryl group by another or by an aryl group is considered as a normal procedure in drug design at which the skilled person would arrive without inventive skills, when looking for further compounds for the treatment of cancer.

Consequently, the subject-matter of present claims 1-8 cannot be considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:

The present application relates to compounds which are useful for the treatment of inflammatory or autoimmune diseases and the subject matter of claims 1-8 is therefore considered as industrially applicable (Article 33(4) PCT).